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Analysis of errors in prefrontal animals in delayed response test

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I

The discovery made by Jacobsen (1936) establishing that delayed responses (DRs) are severely impaired after prefrontal lobectomies in monkeys may be considered as a milestone in our research concerning the functions of prefrontal areas. It is true that much discussion has developed around the question of how Jacobsen's findings should be explained; however the fact itself has been confirmed by all the investigators studying the problem. As is well known, the discussion had originally turned around the question of whether the impairment of the DRs was caused by the deficit of recent memory, as Jacobsen claimed, or by some other mechanisms. The explanation proposed by other authors referred to animals' hyperactivity (Wade 1947), or increased distractability (Malmo 1942, Wade 1947, Harlow et al. 1952), or else to the impairment of associative function (Nissen et al. 1938, Finan 1942), to quote only the most widespread concepts.

Several years ago we undertook the study of the effects of prefrontal ablations on DRs in dogs and cats. This was done in the period after we had already established the disinhibitory syndrome following prefrontal ablations in dogs (dealt with in estenso in

Brutkowski's paper), and the question arose whether the impairment of DRs could be also explained by disinhibition. This required the reproduction of the DR test in the same animals in which the first symptom was found, and if the impairment of this test should be observed also in these animals, then it was hoped that an analysis of it would be easier.

In designing our experiments with DRs we applied a method similar to that originally introduced by Hunter (1913), namely: i. we used the triple choice method instead of the double choice method applied in the studies of the DR deficit after prefrontal lesions; ii. the foodtrays were placed far from each other, separated by an angle of 60 degrees, as viewed from the starting platform; and iii. as preparatory signals, buzzers operating from the respective foodtrays were used (fig. 1). The triple choice enabled an analysis of the

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character of the erroneous responses to be made, since it allowed the animal a double choice between two foodtrays not signalled by the preparatory stimulus. The large angles between the foodtrays permitted us an observation of the postural reactions of the animal during the delay period. The introduction of buzzers as preparatory signals made the whole experimental procedure in many respects analogous to that used in conditioning experiments.

To give some more details concerning the experimental technique,

it should be mentioned that during the delay period the dog was on the leash, and the cat in the small cage, on the starting platform, while during the intertrial intervals it moved freely around the room; in each session the same number of reinforced trials (usually 4 or 5) was given in respect to each foodtray; when the animal made an error, it did not receive food in that trial even if it made a "correction" by running immediately to the proper foodtray; however, in the next trial the same foodtray was signalled, and the animal was released immediately after its presentation, so as to secure the correct response.

Both dogs and cats mastered the rules of the "game" very quickly, and usually after a few preliminary experimental sessions they were fit for regular experimentation.

Our first results obtained on dogs with prefrontal lesions by this method can be briefly summarized as follows (Lawicka and Konorski 1959):

While normal dogs are amazingly skillful in the performance of the DR test, being able to withstand successfully many minutes of the delay period, and the various distractions interposed during it, after the ablation of the prefrontal poles rostrally to the presylvian sulcus the animals become severely incapacitated in this respect. Their correct response becomes largely dependent on the preservation of their bodily orientation assumed in the moment of the action of the preparatory signal. This orientation being changed, the animal is in most cases not able any more to find his way to the proper foodtray.

In consequence all the distractions producing a change of the bodily orientation cause, as a rule, erroneous responses. Since the deficit of the animals was not due to the increased hyperactivity, our prefrontal animals being not hyperactive, nor to the impairment of associative function, which was proved to be quite normal, our first assumption was that the original idea put forward by Jacobsen was right, i.e. the deficit of the recent memory in prefrontal animals was responsible for the impairment of their performance in the DR test. The only reservation we made was that not the recent memory in general was impaired after the prefrontal lesions, but only the recent memory of directional cues (Lawicka and Konorski 1959, Konorski 1961).

However, our further experiments performed on cats with similar technique cast some doubt on this latter interpretation (Lawicka and Konorski 1961). It had been thought that after prefrontal ablations the cats should be rather worse in their DR performance than the dogs were, since they were not in the habit of pointing motionless in one direction for long periods of time. What appeared in fact was something quite the reverse. First, it was found that the animals were able to find their way to the proper foodtray after the delay period in spite of the fact that they did not keep their bodily orientation in its direction. Nevertheless, their performance was much worse than that before operation because they made many perseverative errors. The following types of these errors could be distinguished: i, "last response errors" consisting in repeating the last successful response, and: ii, "preference errors" consisting in the increased tendency to

run to one or two particular foodtrays. Secondly, after committing an error, the animals very often attempted to correct themselves and ran to the proper foodtray, where they remained for a considerable time waiting for the presentation of food (which, of course, was not offered to them). Thirdly, in the course of experiments the animals gradually improved their performance by being more and more able to inhibit their perseverative tendency.

These findings have clearly invalidated the Jacobsenian interpretation of the DR deficit after prefrontal lesions, at least as far as cats are concerned. However, it was hardly acceptable that a deficit of the same function would have a quite different mechanism in cats and dogs. Therefore, it was necessary to re-examine the DR impairment in dogs in order to see whether the same mechanism of this impairment is here in operation as that discovered in experiments with cats.

The clearest finding obtained in the DR performance in our prefrontal dogs was the deleterious effect of distractions applied during the delay period. It had been found that while without distractions the animals could solve this test even after a considerable delay period (amounting to several minutes) owing to their ability to preserve the bodily orientation towards the proper foodtray, any distraction producing a change of this orientation momentarily reduced their performance to the chance level. It was further proved that this impairment was permanent, at least in our experimental condition. Therefore, it was thought that this very type of experiment was

suitable for our analysis.

II

We present here a detailed analysis of a long series of experiments with distractions performed in one of our dogs. Before operation this dog was carefully studied in many DR tests and his performance, even in the most difficult tasks, was excellent. After operation he gradually learnt to react properly after a 1 min. delay but this was due to the fact that the animal had acquired a habit of facing motionless the proper foodtray throughout the delay.

In the present series we applied a distraction which had been frequently used before since it appeared to be most convenient for several reasons. The distraction procedure was as follows: 15 sec. after the operation of the preparatory signal (the buzzer on the given foodtray sounding for 3 sec.) the bowl with food was placed on the platform, and small pieces of food were dropped by the experimenter during 15 sec. The animal while eating food had to turn back to the room loosing any previously assumed bodily orientation. After a further 30 sec. the animal was released. If he went to the proper foodtray, the trial was completed and a new distraction trial started after 2 min. If his run was wrong, then after 2 min. a correction trial was given in which the dog was released immediately after the sounding of the same buzzer. Of course in such a case the animal reacted always correctly. Only then after a 2 min. interval was another trial with distraction given.

It is clear that such a distraction could be applied indefinitely

since the animal did not become habituated to it and he must have changed his bodily orientation for the period of eating.

In fig. 2 the whole period of experimentation in which the

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distractions were applied is represented. Each block of 4 sessions with distractions (each session consisting of 15 reinforced trials) was alternated with a similar block without distractions. We can see that while the blocks without distractions became in this period of experiments almost correct, in the blocks with distractions the performance is on the chance level, and does not improve in the course of experiments.

If we analyse, however, the errors the animal committed in more detail, we may see that his responses were far from being random. As seen in Fig. 3, in which the erroneous responses to various foodtrays

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in each block are represented, the animal very quickly developed severe perseveration consisting in approaching mainly the left foodtray. Thus, whenever this foodtray had been signalled by the preparatory stimulus, the animal's response was correct, but when other foodtrays were signalled, the response was wrong. This was the cause of 2/3 erroneous responses and the apparent chance level of the animal's performance. It is further seen that at the beginning and at the end of the series, the animal sometimes, instead of going to the wrong foodtray, simply

went nowhere.

It should be noticed that in two other dogs in which a series of experiments with distractions was performed the results were quite the same, except that in those dogs the preferential foodtray was that on the right.

Such behaviour shows that the animals found a kind of pseudo-solution of the task they were confronted with: the fact that 5 times in each session the run to the left foodtray was reinforced equalized the whole experimental set-up to that of irregular reinforcement, that is, a situation in which, as is well known, the response becomes very resistant to extinction.

In view of the results obtained in our experiments with cats it was assumed that the task presented to the dog was not unsolvable for him, but rather made more difficult, and therefore the animal reverted to the simpler, although less effective, solution of running always to the left foodtray. In consequence, if we could find a way to inhibit this habit, then perhaps the proper solution of the problem could be achieved.

One of the ways of inhibiting the habit of going always to the left foodtray in trials with distractions would be simply to stop applying the left preparatory signal. In this way the run to the left foodtray would never be reinforced and ~~in this way~~ would be subjected to regular extinction. This method was indeed used with success in one of the series of experiments performed on a prefrontal cat (Fig. 4).

However, it was thought that more profitable would be to preserve

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the triple choice method, since it secured the proper analysis of errors committed by the animal. Taking this into account another procedure was adopted which ran as follows:

After each successful response in trials with distraction, a number of "sham trials" were given: the animal being attached on the platform received food in the bowl, exactly as in the trials with distractions, and then, after 30 sec., he was released. In other words the sham trials differred from the true ones in that no preparatory signal was given.

Here at once a clear difference between the prefrontal dog and a normal one became manifest. While a normal dog in the absence of a preparatory stimulus either remains where he is, or, at the most, approaches some foodtray only a few times, the prefrontal dog ran to various foodtrays again and again in many successive sham trials (Fig. 5). We adopted such a rule that the sham trials were repeated until the

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animal did not go to any foodtray on release, but remained on the platform. Only then was the following true trial with distraction given. But at the beginning of this training running to the foodtrays in sham trials was so persistent that we had to repeat them 15 times in succession and then, although their extinction was not achieved,

a true trial was given. In view of so many sham trials being required after each true trial, in the first sessions of this series only 5 true trials were given, otherwise a session would last too long.

Insert Fig. 6 about here

Fig. 6 represents the mean number of sham trials with positive responses in each 15 trials. It is seen that gradually, although very slowly, the reactions of approaching the foodtrays in the sham trials decreased and eventually dropped almost to zero.

Insert Fig. 7 about here

In Fig. 7 the distribution of the runs to various foodtrays in sham trials is shown. It is seen that the overwhelming majority of runs fall on the left foodtray, and only in the last block is this preference no longer seen. It should, however, be noted that even in the period of the strongest preference of runs to the left foodtray, in the sham trials following immediately the true trials the animal simply repeated the same run which was just reinforced, i.e. he made for the most part "last response errors".

What was the effect of the above procedure on the animal's performance in true trials with distractions?

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As is seen in Fig. 8 the effect was immediate and very prominent. The number of errors dropped significantly so that in some sessions no

errors were committed at all. When we returned to the original method of conducting experiments (without sham trials), the improvement appeared to be lasting. It is worthwhile to note that now the few errors committed by the animal were nearly always last response errors and no more preferential errors were made.

III

The experimental material presented in this paper, supported by analogous findings published elsewhere (Lawicka and Konorski 1962 a and b) and by our earlier data obtained on cats (Lawicka and Konorski 1961) allows us to draw the following conclusions concerning the character of the impairment of DR in prefrontal animals.

First, we have seen that even in most severe cases of the DR impairment, as produced in trials with distractions, the correct response is obtainable whenever the appropriate experimental procedure is applied. This fact indicates that the recent memory of directions is not abolished by the prefrontal lesions.

Secondly, we have many evidence to show that the majority of errors committed by the animals in the DR test have a perseverative character, and consists either in the preference to approach a particular foodtray, or in a tendency to repeat the response displayed in the preceding trial.

The simplest hypothesis which would seem to account for these findings is that ablation of the prefrontal area, or rather some specific part of it, produces an increase of perseverative tendency which blocks

the correct DR performance. This hypothesis was proposed by other authors (cf Settlage et al. 1948, Mishkin et al. 1962) and was also put forward in our earlier papers (Lawicka and Konorski 1961, 1962 a and b). It seems however, that this hypothesis is untenable for the following reasons.

First, in recent experiments by Lawicka and Mishkin (unpublished) it has been shown that in an experimental situation quite similar to that described above the prefrontal dogs did not exhibit any perseverative tendency in a test which did not involve the DR. The dogs were trained to go to the left or right foodtray in response to two tones sounding from a loudspeaker located in front of the animal. The task appeared to be very difficult and the dogs mastered it after a considerable number of trials. Nevertheless, the prefrontal lesions did not produce any deficit in this test, neither did the animals display any perseverative tendency even if the response to the same foodtray was reinforced several times in succession. On the other hand, the same animals were strongly impaired in DRs with distractions, and in this very test they exhibited a strong perseverative tendency (fig. 9). It should be added that in normal animals the DRs with distractions

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are much easier than the go-left, go-right differentiation to non-directional sound stimuli, and the performance of the former test is much better than that of the latter one.

These data show that the perseverative tendency itself is not increased after prefrontal ablations, and that in our experimental condition it is manifested only in DR tests.

By the way it should be noticed that the above findings disprove the hypothesis put forward by Stanley and Jaynes (1949), according to which the impairment of DRs in prefrontal animals is due to the lack of inhibition of incongruent responses ("act disinhibition"), and another hypothesis claiming that prefrontal animals exhibit an increased "positional habit" (cf. Mishkin, Procop and Rosvold 1962). Indeed, neither "act disinhibition" nor increase of the positional responses is seen in the just described test in prefrontal animals.

Secondly, it should be emphasized that the perseverative tendency appears in normal subjects in all those cases in which the cue for the given response is not clear enough, as is the case in the first stages of discrimination training , or in unsolvable situations throughout the training ("hypothesis" of Krechevsky 1932).

Thirdly, perseveration symptoms appear in abundance in human pathology after damage in various parts of the brain, and take different forms depending on the site of lesion. According to our observations made in the Neurosurgical Clinics of the Polish Academy of Sciences (unpublished experiments of Konorski et al.) different forms of aphasia produce perseveration in different types of responses. And so, patients suffering from the so called "amnesic aphasia", display a strong perseveration in visuo-verbal responses, i.e. in naming objects or pictures presented to them. On the other hand, patients suffering from

"sensory aphasia" producing the impairment of comprehension of speach display not less strong perseveration especially in audio-gestural responses, consisting in indicating objects after hearing their names, or fulfilling orders. The patients suffering from so called "conductive (or central) aphasia" encountering great difficulties in repetition of the words heard manifest a tendency to perseveration especially in audio-verbal responses.

And so we see that after the focal lesions of the brain producing the impairment in the particular systems of reactions, the perseverative errors may be chiefly or exclusively found in that system which is impaired.

To sum up, we may conclude that we have hardly any evidence to believe that the "increased perseverative tendency" represents a primary symptom produced by the brain lesion which is responsible for the given disorder either in learning of the given task or its performance. Rather the opposite seems to be true, namely that the perseverative tendency appears as a secondary adjustment of the animal to a partially or totally unsolvable task presented to him. This may happen either when the given system of discriminative responses is not yet developed (or cannot be developed at all), or when it is impaired by an appropriate brain lesion.

If so, then we should look for explanation of the poor performance of the DR test by prefrontal animals not in the increased perseveration, but rather in the impairment of some mechanisms intrinsically involved

in the DR procedure. Two alternative hypotheses of such an impairment may be advanced.

1. According to the first hypothesis the essential factor producing the deficit in DR performance of the prefrontal animals would be the weakening of reflexogenic strength of the trace stimulus determining the direction of the animal's response after release. This hypothesis may be directly inferred from our above discussion of the origin of perseverative symptoms, in which we have stated that these symptoms are closely connected with the impairment, or poor development, of the given system of responses. Since, as we have seen, perseveration in prefrontal animals affects only those discriminative responses which are elicited by trace stimuli, the conclusion may be drawn that precisely these stimuli do not provide sufficient cues determining the animal's response in the DR test, i.e. that their reflexogenic value is diminished.

It would be important, too, in this place to emphasize the essential difference between the view proposed here and the old concept of impairment, or abolition, of the recent memory after prefrontal lesions. According to the latter concept the traces of the preparatory signal are more transient than in normal animals, i.e. the animal simply <u>forgets</u> more early where he should go when released, and therefore reacts on the chance level or nearly so. According to our view the impairment of animal's responses has nothing to do with forgetting, since, as shown in our experiments, the correct response may occur after the same delay period as in normal animals. However, the trace of the preparatory

signal is now weaker as the CS than it was before and cannot stand the competition with other intervening stimuli.

Let us try, on the basis of this hypothesis, to explain the DR disorders found in our studies.

In the DR procedure the instrumental response (approaching the appropriate foodtray) is elicited by a component stimulus composed of 1. the trace of the preparatory stimulus, and 2. the actual stimulus of release. As well known from the Pavlovian studies on compound conditioned stimuli (Pavlov 1940), the stronger component of the compound overshadows the weaker component so that the CR to the latter one (when it is applied alone) is much reduced, or even non-existent. Now, we assume that in normal animals the trace CS left after the preparatory signal is as strong as, or even stronger than, the release stimulus, and therefore it can determine the animal's responses. And so, in normal trials the animal reacts in most cases correctly and in the sham trials (when only release stimulus is given) it does not react at all.

But when, owing to the prefrontal lesions, the reflexogenic strength of the trace stimulus is reduced, the actual release stimulus acquires the leading role, while the trace stimulus is now overshadowed by it. But since the release stimulus cannot by itself determine the direction of the response, the animal is confronted with a partially unsolvable task and acts under the simple instrumental conditioning strategy by repeating those reactions which were recently, or most frequently, reinforced.

Our hypothesis allows also to understand why the animal is able to improve significally his performance when special measures, such as described above, are applied. To turn again to the Pavlovian studies on compound CSi, we know that when the stronger component of the compound is applied alone without reinforcement, while the whole compound continues to be presented with reinforcement, then this stronger component looses its dominant character and the leading role is transferred to the weaker component.

It is easy to see that this is exactly what was done by introducing the sham trials: the releasing stimulus was applied alone without reinforcement so many times that it was completely extinguished, and in consequence the dominant role of the trace of the preparatory signal could be re-established.

The hypothesis under consideration seems to account for many prefrontal symptoms in man, when the patient is not able to act under the instruction given beforehand, although he remembers it perfectly and can easily repeat it (cf. Luria, this symposium). It may be admitted that the instruction given beforehand is nothing else as the trace CS analogous to those dealt with in our DR experiments. Since the reflexogenic value of this stimulus is now reduced, it is not more sufficient for eliciting the proper response, especially when the diverting actual stimuli are in operation.

On the other hand, the present hypothesis cannot obviously explain another major deficit of prefrontal animals concerning reversal

learning (cf. Harlow and Dagnon 1943, Settlage et al. 1956), since in this test we have to do exclusively with actual and not trace stimuli. It may be guessed that either the process of reversal learning is more complex than usually admitted, involving some sort of trace stimuli (such as general programme of reversing) or that it depends on another mechanism represented in other parts of the prefrontal area, or else that the hypothesis now under discussion should be rejected.

2. An alternative hypothesis which may account for our data refers not to the weakened reflexogenic value of trace CSi, as the chief factor of the DR deficit in prefrontal subjects, but rather to the increased reflexogenic value of actual stimuli.

There are many observations pointing out that the animals after frontal lesions display an exaggerated orienting reaction towards the external stimuli. This property of the frontal animals was often referred to as hyperreactivity (cf. Rosvold and Mishkin 1961) and was considered to be responsible for their increased "distractability". In dogs and cats these increased reactions were in fact observed by us particularly when the source of the auditory stimulus was remote from the foodtrays. They were also observed in CR experiments after premotor-prefrontal ablations by Stepien et al. (1960). Generally speaking we can admit that the frontal animals (as well as humans) are more "stimulus bound" than normals. Perhaps one can explain this symptom by supposing that specific parts of the frontal region play a role in suppressing these reactions in the course of habituation, and

that their ablations lead to "dishabituation".

Now, there is again some evidence showing that the orienting reaction towards a stimulus plays a positive role in the process of conditioning. In fact, stimuli producing stronger orienting reactions are easier conditionable than those producing weaker reactions, and the CRs established to them are more stable and resistant to extinction (Pavlov 1940). In consequence one can admit that prefrontal animals are not less, but rather more prone to develop conditioned responses, and these responses may become more strong and resistant to extinction than in normal animals.

This reasoning seems to explain satisfactorily our data concerning the DR deficit in prefrontal animals. In our experiments the DR is always preceded by the immediate stimulus provided by the releasing procedure. If the animal, after being released, goes to the proper foodtray and receives food there, the bond between the releasing stimulus and the response may become stronger in the prefrontal animal than in the normal one, hence the increased tendency to repeat this response in the same condition. This is the source of perseverative errors observed so often in our prefrontal cats. After performing such an "unwanted" conditioned response the animal is able to go to the proper foodtray, since the trace of the preparatory signal is totally preserved.

Since the perseverative responses are not reinforced by food they eventually become extinguished and in consequence the animal's DR performance is gradually improved.

The handicap of cats in comparison with dogs in the DR test is that they are usually not able to preserve their bodily orientation if the delay period amounts to one minute, or so. Therefore, their performance in DRs without distractions is poorer than in dogs. However, when in experiments with dogs the distractions are introduced interfering with their bodily orientation, then their performance, as we have seen, is strongly deteriorated, but again this deterioration is based on the same principle as before. Now, presentation of food on the platform plus releasing stimulus become so strongly connected with the given reinforced response that the animal performs again and again this very response instead of the correct ones, the more so that from time to time it is indeed reinforced. The strength of the bond established between the distractive stimulus and the response in the prefrontal animal is best proved by the exceedingly strong resistance to extinction of this response in sham trials, as compared with the normal animals (cf. fig. 5). However, when after many sham trials extinction is reached, we observe the immediate improvement of the animal's DR performance showing again that his recent memory of the preparatory signal is not impaired.

The hypothesis presented here, in contradistinction to the previous one, allows to account not only for the data described in this paper but also for the large body of evidence showing that, while the prefrontal animals are generally as good as the normal ones in original discriminative learning, they are dramatically impaired in any reversal of discrimination, as shown long ago by the Harlow group.

The difficulty in reversal learning would be simply explained by the abnormal strength of the conditioned connections established in the original training.

Conclusions

The chief aim of the present paper was to discuss various hypotheses concerning the disorder of the DR performance in the prefrontal animals as revealed in our experiments on dogs and cats. It was shown that the concept of the deficit of recent memory being the essential factor of the DR impairment cannot be true, since according to our experimental evidence this deficit does not exist. The theory of "act disinhibition" also cannot be held since this sort of inhibition is not impaired even in much more difficult discrimination tests. It also seems that the impairment cannot be due to the increase of positional habits. It has been shown that increased perseverative tendency manifested by prefrontal animals in the DR test cannot be considered as the cause of the defect, since it does not appear in these animals in other discrimination tests and does appear after nonfrontal lesions. It was suggested that perseveration is a secondary symptom related to the impairment, or poor development, of a given system of responses.

Two alternative hypotheses satisfactorily explaining DR disorders in prefrontal animals were discussed: one of them attributed these disorders to the decrease of reflexogenic strength of trace CSi, while the other one pointed out to the increase of the reflexogenic strength of the external stimuli as the chief factor disturbing the DR. The

latter hypothesis seems to cover not only the DR deficit but also the impairment of reversal learning observed in prefrontal animals, while the former one does not.

It should be added that the two hypotheses presented here do not mutually exclude each other, and it may be supposed that both the mechanisms discussed above can be jointly or separately in operation, depending on the exact localization and/or extent of cerebral lesion.

PREFRONTAL CORTEX AND DRIVE INHIBITION

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The first evidence that frontal cortex represents a higher level of control of the autonomic nervous system and affective behavior was clearly shown by Fulton and his collaborators in their fundamental work on primates /1948, 1951/. Central representation of the viscera and emotionality had, however, concerned many earlier investigators. Most of them regarded the motor and pre-motor corteces as regions subserving both somatic and visceral mechanisms. As long ago as in 1876 Bechefontaine showed that electrical stimulation of the sigmoid area in the dog exerts an inhibitory influence on the gastric motility and facilitates the peristalsis of the lower part of the alimentary tract. These findings thereafter were extended by Openchowski

students who observed that the tonus and movements of the small intestine and colon were changed in response to the stimulation of the vicinity of the cruciate sulcus. The relation of the pre-motor cortex to the alimentary system was also confirmed in numerous stimulation studies carried out on monkeys, dogs and cats during the last few decades /Watts and Fulton 1934, Kennard 1944, Davey, Kaada and Fulton 1950, Babkin and his co-workers 1950, 1951, and others/. In addition, it has been pointed out that the orbito-frontal region is involved in the activity of the gastro-intestinal tract. Thus Magoun, Hanson and Fisher /1933/ produced chewing by electrical stimulation of the "most anterior regions just below the cortex of the anterior composite gyrus /orbital gyrus/" in the cat, whereas Bailey and Sweet /1940/ demonstrated slowing or arresting the gastric tone from stimulation of the Walker's area 13 situated in the orbital surface of the monkey's frontal cortex.

In addition to the gastro-intestinal alterations obtained by orbital surface stimulation, changes in respiration, blood pressure and thermal regulation have been reported in animals and in man both in the past /Preobraschensky 1890, Spencer 1894/, and more recently /Delgado 1948, Livingston 1948, Livingston, Chapman, Livingston and Kraintz 1948, Kaada 1951, Anand and Dua 1956, Newman and Wolstencroft 1960, and others/. Delgado and Livingston /1948/ have found that "the sulcus principalis in the monkey and the sulcus presylvius in the dog contain zones of cortex ... where pure excitation as well as zones of cortex where pure inhibitory

responses, including apnoe, occurred. The inhibition obtained by stimulation of the hidden cortex within the sulcus presylvius is complete and of long duration in contrast to only partial effect obtained by stimulation of the orbital surface."

Another frontal area which appears to be intimately associated with visceral functions is the mesocortical cingulate gyrus, particularly its rostral portion, including the pre-callosal /genual and sub-genual/ sectors. Experimental studies in this respect were initiated by Smith /1945/ who found that a complete relaxation of the muscles and a variety of autonomic manifestations followed electrical stimulation of this area in the monkey. In addition, vocalization was produced. Since all these reactions ~~usually~~ occurred in conjuction with many emotional expressions, the author concluded that the cingulate area was concerned with organizing affective behavior.

The cingulate gyrus in the dog and in the cat has also been shown to have a strong autonomic representation /Kremer 1947, Akert, Hess and McDonald 1951, Hess, Akert and McDonald 1951, Löfving 1961/. Babkin and Speakman /1951/ demonstrated that stimulation of the sub-genual portion of the anterior cingulate gyrus in dogs produced inhibition of the strength of pyloric peristalsis, and a slight fall of the tomus.

Experiments performed with ablation technique have shown less remarkable alterations of visceral functions in frontal animals. Although there is considerable evidence that after lesions of the motor or pre-motor cortex

intestinal tract and other internal systems do occur /Mettler, Spindler, Mettler and Combs 1936, Bulygin 1941, Hesser, Langworthy and Kolb 1941, Bykov 1957, Galperin 1961/, and definite changes in salivation /Aleksandrov 1949, Kravina 1956/, rumination cycle /Bell and Lawn 1956/, micturation /Langworthy and Hesser 1936/, diuresis /Komendantova 1939/, thermal regulation /Aleksandrov 1949/, and many other activities have been reported, ablation of the prefrontal cortex in most instances fails to produce defects of this sort /the only chronic change following excision of orbito-frontal cortex was demonstrated by Delgado /1948/, and Delgado and Livingston /1948/, and refers to an elevation of the temperature of the extremities/. This may indicate that however portions of the medial and basal prefrontal cortex are implicated in the functions of the viscera, all basic activities of the internal organs are primarily co-ordinated at other levels of the brain. Therefore the effects of prefrontal lesions upon the viscera are very transient or escape the experimental analysis.

Emotional changes resulting from frontal lobe ablation were for a long time overshadowed by the deficits in intellectual capacities. Although one finds a few suggestive descriptions of such changes in earlier reports, it was again Fulton's group which has accumulated a large body of evidence that frontal lobes pertain to feeding, fear and angry behavior. Thus Fulton, Jacobsen and Kennard /1932/ have reported that after extensive frontal damage in the monkey "an increase in appetite occurs which sometimes involves ingestion of two to three times the normal amount

of food". Watts and Fulton /1934/ showed that bilateral partial or complete ablation of the frontal lobes caused morbid hunger and, occasionally, intussusception. Kuch and Shenkin /1943/ found only a slight increase in food intake after removal of area 13 in the monkey, whereas Langworthy and Richter /1939/ showed that "bilateral lesions of frontal poles made cats ravenous for food". This finding was also confirmed on dogs with prefrontal lobectomies /Afanasev 1913, Shustin 1958, Brutkowski 1959a/, or pre-motor ablations /Bykov 1957/. Anand, Dua and Chhina /1958/ reported that frontal lobe lesions including or restricted to the posterior orbital cortex in monkeys and cats produced a decrease in food intake, while those which spared the posterior orbital cortex were followed by an increased food intake.

Increase drive for food has also been noticed in man after surgical removal of the anterior and medial portions of the frontal lobes, extirpation of frontal tumors or frontal lobotomy. Bulimia in cerebral tumors and injuries was found a long time ago, but only neuropathological studies during the past 30 years have demonstrated that in a considerable number of cases excessive hunger may be associated with frontal lobe syndrome /Kirschbaum 1951/. Many authors point out that changes in eating behavior in man are particularly striking when the lower medial or orbital quadrants are severed /Hofstatter, Smolik and Busch 1945/. Kirschbaum /1951/ suggests that the extensive hunger in frontal patients "may be attributed to the loss of cortical control over autonomic diencephalic system".

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Disease or damage to the frontal lobes in man may also release other forms of emotions which are normally suppressed. One of the frequent symptoms described in human frontal patients is a sexual disinhibition /Jarvie 1954, Häfner 1957, Lauber 1958, Silikiewicz 1960/.

Observations on frontal animals have been rather scanty in this respect since sexual changes may have passed unnoticed owing to a failure of relevant evaluative experimental procedures.

Changes in behavior associated with anxiety states or fear and aggressiveness following frontal lobe damage have however been reported in many instances both in man and animals. Within the past twenty five years innumerable publications have shown that interrupting the projections arising from the frontal cortex favorably affects depressive and obsessional states. On the other hand, in aggressive cases gratifying results have been obtained after section that involved the anterior cingulate region. Diminution of preoperative irritability, aggressiveness and agitation following this operation in humans strikingly resembles behavioral changes occasionally described in cingulectomized cats and monkeys /Ward 1948, Glees, Cole, Whitty and Cairns 1950, Kennard 1955/. These findings are, however, at variance with another group of observations which indicates that cingulectomized animals develop more aggressiveness and angry behavior immediately after operation /Kennard 1955/56, Miraky, Rosvold and Pribram 1957, Pechtel, McAvoy, Levitt, Kling and Masserman 1958/. Brutkowski, Fonberg and Mempel /1961/ have recently reported that violent rage and anger are released in dogs following lesions of the genual and sub-genual gyri on the medial surface of the frontal lobes. Similar results were reported earlier by Fulton and Ingraham /1929/ who described a marked reaction of rage in previously friendly and playful cats following

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[illegible] in some instances, after selective ablation of the orbital cortex. These findings have recently been confirmed by Auleytner and Brutkowski /1960/ on pre-frontal dogs, and earlier by Bond, Bidder and Rowland /1957/ on cats, as well as by Aleksandrov /1949/ and Bykov /1957/ on dogs with damage to the premotor cortex.

-7

In many respects the resulting changes in emotionality resemble those of the decorticated preparation /Cannon and Britton 1925, Bard 1934/. This has given ground for the supposition that frontal regions may mediate an effect inhibitory effect on the hypothalamus and the phylogenetically old cortex within the limbic system /MacLean's "visceral brain, 1949/. Recent neurophysiological and experimental anatomical studies provide a good deal of evidence to support this view. Thus the work by Ward and McCulloch /1947/, Le Gros Clark /1948/, Wall and Davis /1948/, Meyer, McLardy and Beck /1947/, Le Gros Clark and Meyer /1950/, Wall, Glees and Fulton /1951/, Auer /1956/, and Nauta /1960/ has demonstrated powerful reciprocal fiber connections between the medial orbito-frontal and pre-motor cortex via the medial forebrain bundle or a relay in the nucleus dorsalis thalami /pars medialis/ with the dorsomedial, ventromedial, paraventricular, anterior, and lateral hypothalamic regions. On the other hand, it has been shown that the rostral limbic cortex is linked with the entire ventro-medial frontal cortex which might be classified as a portion of the extralimbic system /Pribram and MacLean 1953/, whereas studies by Adey /1952/, Adey and Meyer /1953/, and more recently, by White, Nelson and Holtz /1960/ suggest a connection between the medial frontal cortex and the hippocampal formation through the cingulum fasciculus.

The presence of a definite anatomical association

hypothalamic nuclei is of considerable importance. It would provide an anatomical basis for the behavioral finding relating both frontal lobes and hypothalamic centers to the control of feeding and fear behavior.

In recent years a group of workers from the Department of Neurophysiology of the Nencki Institute of Experimental Biology in Warsaw has undertaken an investigation on dogs with damage to the prefrontal cortex [x]. Initially, a bilateral amputation of frontal

[x] According to Kreiner /1961/ the term prefrontal cortex will be used here for the areas delimited by the anterior rhinal fissure, the bottom of the presylvian fissure, its prolong-ation over the dorsal ridge of the hemisphere, and, on the medial aspect of the hemisphere, by the genual fissure and its prolongation ventrally from the genu of the corpus callosum.

Although, anatomically, the role of the prefrontal cortex in subprimates is depreciated, experimental evidence suggests that, in the cat and dog, the electrically inexcitable cortex situated anterior to the pre-motor areas contributes to many forms of behavior attributed to the prefrontal cortex in higher species. Therefore, functionally, the term "prefrontal cortex" seems to be justified to be used in certain lower mammal species, including cat and dog.

poles anterior to the presylvian sulcus /Figs. 1 and 14A/.

Figure 1

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was performed, and it was found that this lesion produced a marked, though temporary, impairment of the preoperatively trained inhibitory conditioned reflexes /CRs/ in a situation in which positive responses were reinforced either positively /by the presentation of food or water/, or negatively /by the application of electric shock to the animal's leg, or introduction of acid solution into the animal's mouth/. It also was demonstrated that the postoperative deficit in inhibitory trials, which has been designated by the term "disinhibition" according to Pavlov, was, with certain exceptions, of almost the same order both in the type I /classical/ and type II /instrumental/ conditioning /Konorski, Stepien, Brutkowski, Lawicka and Stepien 1952, Brutkowski, Konorski, Lawicka, Stepien and Stepien 1956, Brutkowski 1957, 1959a,b,c, Lawicka 1957, Auleytner and Brutkowski 1960, Brutkowski, Fonberg and Hempel 1960, Cernicki 1961/.

All testing was conducted on male mongrel dogs in a Pavlovian frame mounted within a sound-proof conditioned-reflex chamber. Preoperatively, the animals received extensive training in differentiation, conditioned inhibition, and alternation tasks, using conditioned stimuli /CSs/ of different modalities /acoustic, visual and tactile/ in successive order. A positive or excitatory CS was presented several times during the testing session, whereas a negative or inhibitory CS

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All testing was conducted on male mongrel dogs in a Pavlovian frame mounted within a sound-proof conditioned-reflex chamber. Preoperatively, the animals received extensive training in differentiation, conditioned inhibition, and alternation tasks, using conditioned stimuli /CSi/ of different modalities /acoustic, visual and tactile/ in successive order. A positive or excitatory CS was presented several times during the testing session, whereas a negative or inhibitory CS was used once or twice per day. The conditioned inhibition test described in this paper was a combination of two successively presented stimuli, viz. the conditioned

CI-CS compound was not reinforced, whereas the CS itself, if it was used separately, was followed by reinforcement, and it then produced a positive response. In the initial training the animals responded positively to the CS within CI-CS compound as well. However due to the lack of reinforcement the latter response was inhibited after a few experimental sessions. It is worth mentioning that the CI never produced a response x/. Originally, both stimuli

x/ The total or partial failure of responding to CI from the very beginning of testing becomes understandable in view of the concept of primary inhibitors developed by Konorski and Szwejkowska /1952/.

were used in immediate succession. Thereafter, an interval of one second was inserted between the components of the CI-CS compound, and it was progressively extended up to several seconds.

In the alternation task a CS, which was presented in a successive order with ca. 1 min. intertrial intervals, was alternately reinforced and not reinforced, that is, it was associated with the unconditioned stimulus /US/ in the first, third, fifth etc. trials, but it was not followed by reinforcement in the even trials xx/.

xx/ Ławicka /unpubl./ has recently shown that the alternation task may be regarded as a particular form of conditioned inhibition procedure.

Training of instrumental /type II/ CRs was made according to Konorski and Miller's procedure /1936/. The positive CR consisted of the animal placing its fore leg upon its hind leg upon an elevated board situated in front or in back of the animal

respectively; in another study, one animal group was trained to bark in response to the presentation of CS. Correct positive performance was either immediately reinforced, or, if salivary CRs were registered in addition, after a delay of 5 to 10 secs. Correct inhibitory response consisted of refreining from placing the leg on the board or barking within 5 or 10 secs. permitted for response. Each inhibitory trial, no matter whether the CR was elicited or not, was not followed by reinforcement. All trials were separated by ca. 1 min. intervals.

The classical testing procedures consisted of either defensive conditioning reinforced by electric shock, or salivary reflexes trained in situations in which food or acid were used as USi. Salivation was obtained through a fistula of the parotid gland prepared prior to testing according to Sołtysik and Zbrożyna /1957/, and registered by Kozak's technique /1950/. The positive CS was exposed for 20 secs. After the presentation of reinforcement /food or introduction of acid into the animal's mouth/ the CS remained on for additional 5 secs., partially overlapping the US. The unconditioned salivation was recorded as well, and the intertrial intervals were from 5 to 7 minutes. The differential CS, and the CS used in the CI-CS compound were exposed for 20 secs., whereas the CI was presented for 10 secs.

In the classical motor-defensive conditioning the animal responded by flexing its leg whenever the positive CS was presented, and [redacted] received electric shock. In the inhibitory trials no shock was applied to the animal's leg, and the motor response became extinguished.

In certain experiments respiration was graphically recorded in addition to the salivary or motor effects. Furthermore, in acid situation licking movements to the presentation of the CSi were counted. All animals were carefully observed while being tested, and changes of more general aspects of behavior patterns determined by food or fear were also noted.

As mentioned above, following a bilateral prefrontal lobectomy /Fig. 14A [redacted], D-14/ the animals displayed a temporary disinhibition of CRs which had been trained prior to operation. In other words, in the initial postoperative period an impairment on most of the inhibitory trials occurred which was manifested by salivation and positive motor performance in response to the presentation of the differential CS or the CS within the CI-CS compound. If portions of the premotor cortex, including the precruciate and sigmoid areas, were involved in the lesion /Fig. 14A [redacted], D-2/, the impairment was even more conspicuous. In all instances, the postoperative deficit in conditioned inhibition was greater than that in differentiation performance. In some of the prefrontal animals, the differential trials were impaired only once

or twice postoperatively. On the other hand, inhibitory trials in the alternation task were always severely affected. Moreover, in some animals the impairment on this task was permanent /Figs. 2, 3, 4 and 5/. The rate and the amplitude

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Figs. 2, 3, 4 and 5

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of the respiratory rhythm also increased remarkably /Figs. 7 and 8/, and the licking movements during the presentation of inhibitory CSi in the acid animal group were produced at a more rapid rate than before operation /Table I/.

Table I

It must be emphasized, however, that the postoperative disinhibition of inhibitory CSs was in most instances not complete, that is, even in the early postoperative period the salivary or motor effects in the inhibitory trials often differed in duration and intensity from those in the positive trials, and only occasionally did the responses to the presentation of inhibitory CSi attain or exceed the positive level of performance. The response to the CI within the CI-CS compound remained unchanged postoperatively.

In our paper concerning effects of prefrontal lobectomy on the CRs it was said that positive salivary responses were slightly diminished following ablation /Grutkowski 1959a, b/. This is true only for the immediate postoperative period, however, and may be considered a traumatic depression, since in the case of resumption of testing from 7 to 10 days after lobectomy the positive salivary CRs were unchanged or even increased /Fig. 9/.

Fig. 6

They also showed an increase in the later postoperative period.

On the other hand, immediately after lobectomy the instrumental CR often failed to occur. Instead, a variety of primordial food activities was elicited: the animals incessantly sniffed and searched for food within the inter-trial intervals and during the presentation of CS1, they violently grabbed the food, and persisted to lick out the cup after the end of food intake, postponing thus the presentation of the next trial. However, within a few post-operative days the basic food reflexes subsided, and the instrumental response then recovered. This picture was not observed in all frontal lobectomised dogs. In some of them the instrumental food CR was present from the first postoperative days though licking and searching behavior occurred in addition. However, apart from the fact whether or not the instrumental CR was temporarily suppressed after lobectomy, if it was present in response to the CS, it used to occur in the intertrial intervals as well. Since this excess in responding was accompanied by an increase in salivation and other autonomic responses [redacted] it might not be related to hyperactivity, but it rather suggests that, in addition to the impairment on inhibitory performance, the prefrontal lesion produces an enhancement of positive behavioral patterns determined by food drive. More recent observations extended this view upon fear-like behavior. Thus, it has been demonstrated that most of the motor effects evoked in fear circumstances were amplified and associated with increased respiratory rhythm. Many responses were elicited after [a/] shortened latency, and occasionally they persisted

after the end of the trial. This was particularly evident in the animal group trained in classical-defensive CRs /Figs. 7, 8 and 9/. Following prefrontal lesion these

Figs. 7, 8 and 9

animals became strikingly fearful during testing. They tried to escape or bite when approached, and showed many other defensive-offensive reactions. They also became more sensitive to electric shock or acid reinforcement, and the volume as well as the rate of unconditioned salivation in the acid animal group were remarkably magnified /Fig. 10/.

Fig. 10

The failure of postoperative increase in some conditioned and unconditioned reactions in a small number of animals may be supposed to be due to a maximal level reached by these reactions already prior to lobectomy, and does not speak against the general finding indicating that the post-operative increase in positive reactivity determined by affective behavior is apparent. Also the instrumental food areflexia, which occurs at the early postoperative stages, need not suggest a reduction of previously acquired feeding patterns, the more so, since it is replaced by a variety of viscero-somatic and emotional activities directly related to food situation. It is clear that in the early postoperative period the increased drive for food interferes with performance of the instrumental response, later, however, as the postoperative increase in the drive for food becomes reduced, it is possible for instrumental response to be elicited.

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Similarly, an impairment on the avoidance habit described in frontal animals does not necessarily reflect a diminution of anxiety (Wojtonis and Brutkowski 1960, Kaner 1960, Wolf 1962, Wojtonis-Antonowa and Brutkowski 1962, Soltysik

and Zielinski 1962 [illegible] been postulated by a few investigators /Lichtenstein 1950, Streb and Smith 1955, Pribram and Weiskrantz 1957, Waterhouse 1957/. Our findings indicate that prefrontal lesion produces a sentisisation to reinforcement. Since noxious stimulation is absent when avoidance procedure is used, it is not surprising that post-operative changes described in classical defensive behavior do not occur under avoidance conditions. It is also likely that the temporary impairment on the food instrumental or avoidance performances with little or no sign of disturbance in positive classical defensive CR after frontal ablation may be attributed to the destruction of the instrumental reflex arc /Brutkowski 1959b, Auleytner and Brutkowski 1960/, and results from a damage to the most anterior portion of the medial forebrain bundle by means of which the frontal poles maintain conncetions via the hypothalamus with the midbrain. It is postulated that there may be a motivational system in this bundle /Miller 1958, 1960, Olds 1958, 1960, Morgane 1961a, b/ which, when destroyed, abolishes an animal's "urge" to work for food though it has no effect on feeding behavior. This conclusion gains strong confirmation in our findings obtained on prefrontal dogs as well as [illegible] in those recently demonstrated by Balińska /1962/ and Lewińska /1962/ which indicate that following medial hypothalamic lesions in the rabbit a loss of instrumental response motivated by food reinforcement occasionally occurs despite increased food drive.

without increasing food-directed activity

Due to the evidence that both the behavioral patterns

related to [illegible] CRs as well as URs increase after prefrontal lobectomies, it would be erroneous to conclude that prefrontal cortex is primarily concerned with maintenance of correct inhibitory performance, and that postoperative increase in emotionality and conditioning might simply derive from disturbance in the inhibitory activity. It may rather be thought that disinhibition of the inhibitory CRs is a secondary effect which tends to occur due to an enhanced drive level and "release" of mechanisms which are normally suppressed. This suggestion is supported by the further finding that in some instances a conspicuous increase in positive performance may be noticed, while inhibitory responses are left intact /Fig. 11/. Hence, prefrontal cortex which appears to be tied up with hypothalamic nuclei and which includes autonomic control centers may be considered a region

Fig. 11

intimately concerned with modulating the drives and affectively motivated behavior. Since conditioning routines generally involve drive mechanisms, destruction of prefrontal cortex results in an increase of unconditioned reflexes as well as in an elevation of positive CRs and disinhibition of inhibitory CRs.

The evidence that all these changes are transient indicates that the integration of affectively determined behavior patterns is elaborated primarily at the subcortical level, while [illegible] with the regulation of these mechanisms is maintained by the frontal cortex.

This conclusion involves important theoretical and practical implications since an appropriate regulation of drives and emotions plays a highly essential part in human social relationships. Moreover, this capacity in man is primarily learned for it is known that emotions of young people are apparently less controlled. Increase in regulation of emotional patterns from animal to man, and from human child to an adult coincides with the anatomical development of the frontal cortex. However, no conclusive data are available to show that a drive suppression capacity progressively develops in the phylogenetical aspect among the vertebrates. Failure of consistent data of this kind is not altogether a surprise for normally, drive control in animals seems to depend on a variety of environmental circumstances rather than on the level of phylogenetical development, and, secondly, for adaptive purposes an elevation of drives is essential in most instances. It is apparent though that in normal animals the drives are reduced under certain conditions, e.g. a satiated animal fails to exhibit feeding patterns, and a pregnant female loses its sexual desire. As it has already been pointed out, lesions placed in the frontal lobes affect some aspects of these adaptive adjustments rendering an animal seriously impaired on regulating its defensive and food unconditioned and conditioned responses, as well as its behavior related to searching food and to the cessation of food intake.

found that frontal lesions affect differentiation learning.

Within the past few decades several

Kalischer /1909/ was one of the earliest writers to show this impairment in dogs trained in a food experimental situation. The author demonstrated that animals which had preoperatively been trained to pick up a piece of meat to the presentation of a tone /"Fresston"/, and to withhold this response to another tone /"Gegenton"/, became severely impaired on the inhibitory trials following frontal lobectomy since they were no longer able to refrain from responding to the differential tone. Kalischer called this impairment a "disinhibition", and thought it might be produced by an encroachment on the striatum. Further, Afanasev /1911/ reported a disinhibition of inhibitory motor-classical defensive CRs in prefrontal dogs trained in a situation in which the positive defensive CS was reinforced by electric shock. In addition, some of his prefrontal animals exhibited a striking irritation and increased food intake. Aiming at more precise definition of consequences of frontal lobe damage the author also demonstrated that prefrontal dogs were not impaired in learning a discrimination task in which no requirements for inhibitory performance was involved, namely in a situation in which two stimuli presented in successive order were associated with two motor responses and each correct response was reinforced by shock. This finding indicates that animals with damage to the frontal cortex are in fact able to discriminate stimuli and perform relevant positive responses to their presentations, but they have abnormal difficulty in inhibiting the positive response in inhibitory trials in a situation determined by fear or food cues. Our results fully confirm this conclusion. Also the recent work by Shustin /1958/ lends credence to this point of view.

Further insight into the frontal lobe functions has been gained by investigating the animal behavior after partial lesions.

Most recent studies on monkeys suggest that frontal cortex is concerned with at least two types of inhibition /Brutkowski, Mishkin and Rosvold 1960, 1961/. Thus, it has been found that lesion of the dorso-lateral frontal lobe impairs the type of inhibition which enables the animal to shift between two response sets /Rosvold and Mishkin 1959/. In consequence, the dorso-lateral monkey perseverates one response set despite non-reinforcement which is essentially congruent with the findings of Lawicka and Konorski /1961/ in their investigations on prefrontal cats and dogs. These experiments were later extended by Lawicka, Mishkin, Kreiner and Brutkowski /1962/ who showed that delayed-response deficit in prefrontal dogs, which might be considered an example of perseveration, followed the sole ablation of the preeal gyrus situated in the most dorsal part of the frontal lobe.

As to the second type of inhibition, namely that mediated by hypothalamic mechanisms, and as shown above, impaired by prefrontal lobectomies in dogs, it has been reported /Brutkowski, Mishkin and Rosvold 1960, Butter, Mishkin and Rosvold 1961/ that, in the monkey, it is associated with the orbito-frontal region. This evidence underscored the need for a more precise location of this sort of inhibition in the frontal cortex of the dog. Until recently, however, this was obviously complicated by failure of relevant anatomical indications as to subdivision of the frontal cortex in this species. Fortunately, the work

of Adrianov and Mering /1959/, and Kreiner /1961/ provided this information. Experimental studies from our laboratory suggest that the medial aspect of the dog's frontal lobe cortex may functionally be correlated with the orbital area in the monkey. Conversely, the gyrus orbitalis of the dog's brain, which occupies the lateral portion of the frontal lobe between the prorsal, presylvian and rhinal sulci, seems to have no relation to the orbital cortex of the monkey and appears to have been named aside from its function.

At least three successful attempts have been made to show that lesions placed in the medial wall of the frontal pole of the dog's brain result in drive disinhibition. In spite of certain differences in testing procedures the impairment was demonstrated after removal of 1/ the genual area situated in front of the genu of the corpus callosum /Brutkowski and Mempel 1961, see Fig. 12/, 2/ the medial subdivision of the praecruciate area /Stępień and Stępień 1961/, and 3/ the pre-genual area /Szwejkowska, Kreiner, Lawicka and Sychowa 1962/. Further studies, however, have

Fig. 12

revealed a difference of opinion with respect to the localization of inhibitory capacities within other parts of the frontal cortex. Since this disagreement may have been derived from differences in methods, some of the details of these studies should be described.

Experiments performed with the conditioned inhibition procedure and with trials separated by ca. 1 min. intervals

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Experiments performed with the conditioned inhibition procedure and with trials separated by ca. 1 min. intervals, in a way previously described for the dogs with prefrontal lobectomies, indicate that impairment on inhibitory trials is solely produced by destruction of the medial frontal cortex, whereas [illegible] lesions of the proreal and orbital gyri on the [illegible] surface of the frontal lobe, or the dorsal

portion of the prefrontal granular area, the inhibitory performance is unaffected /Brutkowski, Kreiner, Lawicka and Dychowa 1962, Stępień and Stępień 1962/.

With the application of a modified conditioned-reflex technique /Brutkowski and Hempel 1961/ Brutkowski and Ląbrowska /1962/ have recently found that disinhibition of preoperatively trained inhibitory CRs in the dog followed not only the medial ablation but also the removal of the dorso-lateral aspect of the prefrontal cortex /Fig. 13/. Our procedure, however, contrasts with the previous one in some essential points. First, we used differentiation instead of conditioned inhibition training, and, secondly, we separated the trials by 15sec. intervals. Furthermore, the training of our animals was intensified by the presentation of 15 positive and 15 inhibitory trials per day. In essence, our procedure is

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Fig. 13

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identical with that used for testing the monkeys /Brutkowski, Mishkin and Rosvold 1961/.

Under our conditions, the animal's task was to place his right fore leg on the food tray to get a food reinforcement whenever the positive CS, a 1000-cy/sec tone was presented, and to refrain from this response to the inhibitory CS, a 700-cy/sec tone. An error was defined as failing to place the leg on the food tray to the positive CS, or placing the leg within the 5 secs. during which the inhibitory CS was used. Preoperatively, the animals were trained to a criterion of 45 correct responses in 50 successive

inhibitory trials. After attaining this criterion all animals were subjected to bilateral, one-stage, partial resections of the cortex. Each animal group comprised from 3 to 4 specimens.

The following six forebrain areas have been selected for ablating:

1./ The lateral portion of the proreal gyrus and the anterior part of the orbital gyrus which, taken together, constitute the dorso-lateral aspect of the dog's prefrontal cortex /Fig. 14 B/.

2./ The cortex of the medial wall of the prefrontal lobe without involvement of the sub-genual and sub-proreal regions x/ /Fig. 14 C/.

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x/ Since lesions including the lower portions of the genual area as well as the subgenual and subproreal areas result in violent rage behavior which hardly permits handling the animals /Bruthowski, Fonberg and Mempel 1961/, they will not be considered here.

3./ The genual area on the medial surface of the prefrontal lobe.

4./ The basal portion of the cortical tissue hidden in the depth of the presylvian sulcus xx/.

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xx/ Results for the presylvian dogs will be discounted since the histological analysis revealed that the lesion severely damaged the white matter in the caudal portion of the frontal lobe and penetrated towards the striatum. Further investigation on dogs with more accurate placement of the presylvian lesion is in progress.

5./ The lateral and medial portions of the proreal gyrus.

6./ The anterior part of the orbital gyrus.

It is seen from Figs. 1 that lesions of the medial surface of the frontal lobes undoubtedly affect the animal's performance on the preoperatively acquired differentiation habit. Selective ablations of the proreal or orbital gyri produce only slight impairment on inhibitory trials, but a combined lesion of these two regions results in a disinhibition of CRs which is similar to that which obtained after medial removals. Operated /posterior cingulate area/ and unoperated control dogs show no signs of impairment.

However, in spite of the fact that both medial and dorso-lateral lesions produce quantitatively about the same impairment on inhibitory trials, the quality of the disinhibition seems to be different depending on the placement of the lesion. From observing the details of the animal's behavior during testing, two types of abnormal response patterns could be easily distinguished in either of these two basic frontal groups. Whereas the animals with medial lesions displayed a remarkable searching behavior within the intertrial intervals and during the presentation of CSi, and also each instrumental response which used to occur between trials was associated with sniffing and chewing, as well as gazing at the cup and licking it, the dorso-lateral animals did not appear to be affected by a similar increased drive for food. These observations force the conclusion that, like in the monkey, two different neural substrates may be required to be responsible for the disinhibition syndrome in prefrontal dogs. They further suggest that only the medial forebrain regions in the dog are concerned with suppression of responses motivated by food reinforcement.

indicating a disinhibition of CRs

after lesions located on the medial aspect of the dog's frontal lobe are clearly consistent with those obtained by other workers from our laboratory. Conversely, the latter do not find a marked impairment on conditioned inhibition habit after dorso-lateral lesions. As mentioned above, it is possible however that this discrepancy in results may be ascribed to differences between the testing procedures. Assuming that the impairment on inhibitory trials in our dorso-lateral dogs refers to a type of disturbance in cortical act-inhibition /Stanley and Jaynes 1949/, it may be thought that the short intervals between trials, as used to be the case under our conditions and also in most behavioral studies on monkeys, facilitate the errors of perseveration. Some of the work now in progress on two animal groups with either short /15-sec./ or long /1-min./ intertrial intervals appears to provide evidence to support this view. As seen in Fig. 13, dogs with dorso-lateral lesions who had preoperatively been maintained on a long interval

schedule of performance showed no disinhibition of CRs.

Although the findings discussed in this report strongly suggest that the medial regions of the dog's prefrontal cortex are implicated in the inhibition of affective behavior and drives, more definite statements will be possible when the classical /e.g. salivary/ conditioned response procedure will be employed in the way it was done with regard to the lobectomized dogs. Such experiment is planned for as pointed above, the

instrumental response does not suffice to define emotional processes. It now seems reasonably clear that only with application of evaluative experimental techniques which involving responses which specifically reflect affective behavior and drives will it be possible to delineate the qualitatively different aspects of inhibitory activities served by different frontal regions. We also hope that more definite evidence may be brought by some additional modifications in test situations. Realizing this, we have recently been engaged in developing a technique on dogs in which the reinforcing stimulus is deprived of the hypothalamic-type component. Other tests, which may prove successful in the analysis of frontal lobe deficit, are referred to a wide range of commonly used discrimination procedures, such as "differentiation of positive conditioned reflexes", go left - go right" habit etc. Since frontal animals appear to be impaired on differentiation tasks involving inhibitory performance, experiments have recently been carried out in this laboratory /Konorski, Lawicka/ to see their behavior on a type of differentiation task in which no inhibitory responding is required. Although abundant experimental material has already been accumulated by the use of some of these methods, it is hard to compare results obtained in different laboratories because of dissimilarities in a variety of details, including species, lesions and testing procedures.